REMARKS

I. Comments on the Restriction Requirement

Claims 14, 15, 16, 28, and 29 (Groups 9, 10, 11, 12, 31, 32, 33, and 34) are methods of using the polynucleotides of Groups 3 and 4. Applicants remind the Examiner of the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products.

With respect to Claims 14, 15, 16, 28, and 29, the Office Action asserts that "the scope of the method claims is not the same as the claimed product inventions" (Office Action, page 4). To the contrary, the process claims **do** cover the same scope as the product claims because they are **dependent claims** of the product claims. A dependent claim necessarily has the same scope or a narrower scope than its parent claim because a dependent claim further limits the subject matter of its parent claim. Therefore, Applicants presume that these method claims will be rejoined, upon determining allowability of the product claims from which they depend.

II. Objections to the Claims

A. Objection to Claims 3-4 and all claims dependent thereon

The Examiner objected to Claims 3-4 and all claims dependent thereon "because claims 3-4 are dependent upon nonelected claims 1 and 2." (Office Action, page 4.) The Examiner suggested that "[t]he rejection can be obviated by amending claims 3-4 to include the limitations of claims 1 and 2, respectively." (Office Action, page 4.) Amended Claim 3 is an independent claim, and Claim 4 depends from Claim 3. Therefore Applicants respectfully request that the Examiner withdraw the objection to Claims 3-4 and all claims dependent thereon.

B. Objection to all the claims

The Examiner objected to "[a]ll of the claims" "because they recite limitations drawn to non-elected inventions" and stated that "Applicant is required to amend the claims to remove these limitations." (Office Action, page 4.)

Applicants traverse this objection. As discussed in *In re Weber*, 198 USPQ 328 (CCPA 1978), it is an applicant's right, by statute, "to claim his invention with the limitations he regards as necessary to circumscribe that invention, with the proviso that the application comply with the requirements of §112." (*Weber* at 331.) The Court has further decided that §112, second paragraph "allows the inventor to claim the invention as he contemplates it." (*Weber* at 331.) The Court further explained that:

> As a general proposition, an applicant has a right to have each claim examined on the merits. If an applicant submits a number of claims, it may well be that pursuant to a proper restriction requirement, those claims will be dispersed to a number of applications. Such action would not affect the right of the applicant eventually to have each of the claims examined in the form he considers to best define his invention. If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the subgenera would be defined by the examiner rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification. (*Weber* at 331.)

Hence, it is improper for the Examiner to require removing the nonelected species of a Markush Group as a condition for examination of the elected claims and species.

III. Rejection of Claims 3-7, 9-10, 12-13, and 49 Under 35 U.S.C. § 101

SUMMARY OF THE INVENTION

Applicants' invention is directed to a polynucleotide encoding a polypeptide ("PAWES-2") containing a region similar to a Type I EGF motif signature and containing two cysteine residues characteristic of this motif. The polynucleotide has a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of

PAWES-2, for toxicology testing, and for drug discovery (see the Specification at, e.g., page 38, line 12 through page 41, line 27). As described in the Specification (page 17, lines 10-30):

> Nucleic acids encoding the PAWES-2 of the present invention were first identified in Incyte Clone 2056178 from the bronchial epithelium cDNA library (BEPINOT01) using a computer search, e.g., BLAST, for amino acid sequence alignments. A consensus sequence, SEQ ID NO:4, was derived from the following overlapping and/or extended nucleic acid sequences: Incyte Clones 2056178 and 2056018 (BEPINOT01), 826303 (PROSNOT06), 1981527 (LUNGTUT03), 1511001 (LUNGNOT14), and 642949 (BRSTTUT02).
>
> In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:3, as shown in Figures 2A, 2B, 2C, 2D, and 2E. PAWES-2 is 332 amino acids in length and has one potential N-glycosylation site at N286; two potential cAMP- and cGMP-dependent protein kinase phosphorylation sites at T203 and T235; seven potential casein kinase II phosphorylation sites at S33, S77, S93, T147, T175, T237, and T310; two potential protein kinase C phosphorylation sites at S113 and S241; and a potential signal peptide sequence from M1 to A39. In addition, the region of PAWES-2 from N285 to H300 is similar to a Type I EGF motif signature and contains two cysteine residues characteristic of this motif. A region of unique sequence in PAWES-2 from about amino acid 50 to about amino acid 59 is encoded by a fragment of SEQ ID NO:4 from about nucleotide 689 to about nucleotide 718. Northern analysis shows the expression of this sequence in various libraries, at least 73% of which are associated with cancerous or proliferating tissue and at least 33% of which involve immune response. In particular, 40% of the libraries expressing PAWES-2 are derived from reproductive tissue, 20% are derived from cardiovascular tissue, and 13% are derived from gastrointestinal tissue.

Claims 3-7, 9-10, 12-13, and 49 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that "the claimed invention is not supported by a specific asserted utility, a substantial utility, or a well established utility." (Office Action, page 5.)

The rejection of Claims 3-7, 9-10, 12-13, and 49 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in human bronchial epithelium tissue. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires

knowledge of how the polypeptide coded for by the polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Applicants submit with this Response the Declaration of Dr. Tod Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the utility of the claimed polynucleotide are without merit.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would [have appreciated on April 29, 1998] that cDNA microarrays that contained the SEQ ID NO:4 polynucleotide would be a more useful tool than cDNA microarrays that did not contain the polynucleotide in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cell proliferative disorders for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15.)

The Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise function.

A. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

B. Uses of the claimed polynucleotide for diagnosis of conditions and disorders characterized by expression of PAWES-2, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion Declaration accompanying this Response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

1. The use of the claimed polynucleotide for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion Declaration. The claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Hillman '725 application on April 29, 1998 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications. (Bedilion Declaration, ¶¶ 12 and 15).[1]

In connection with his explanations, Dr. Bedilion states that the "Hillman '725 application would have led a person skilled in the art on April 29, 1998 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cell proliferative disorders to conclude that a cDNA microarray that contained the SEQ ID NO:4 polynucleotide would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:4 polynucleotide" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on April 29, 1998] that cDNA microarrays that contained the SEQ ID NO:4 polynucleotide would be a more useful tool than cDNA

[1]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Hillman '725 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

microarrays that did not contain the polynucleotide in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cell proliferative disorders for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-April 29, 1998 publications showing the state of the art on April 29, 1998. (Bedilion Declaration, ¶ ¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include more than three (check for sure) pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on April 29, 1998 (and for several years prior to April 29, 1998) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the development of the drug" and how the teachings of the Hillman '725 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Hillman '725 application at the time it was filed "would have wanted their cDNA microarray to have a [SEQ ID NO:4 polynucleotide] because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to April 29, 1998" cDNA microarrays that persons skilled in the art have been doing since well prior to April 29, 1998. (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Hillman '725 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

Nowhere does the Patent Examiner address the fact that, as described on pages 41 and 51 of the Hillman '725 application, the claimed polynucleotide can be used as a highly specific probe in, for example, cDNA microarrays – a probe that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the

claimed polynucleotide. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

The Bedilion Declaration shows that a number of pre-April 29, 1998 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Hillman '725 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Bedilion Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Bedilion Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published before or shortly after the filing of the Hillman '725 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up– or down-regulated is required.
>
> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis in original)

John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Reference No. 1):

In a pre-April 29, 1998 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, (August 1997) Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947 (Reference No. 2) (emphasis added).

2. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., *supra* (Reference No. 1):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Reference No. 1, page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 3); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 4).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose

hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999) (Reference No. 5, see page 683). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 6), indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the

Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be withdrawn regardless of their merit.

3. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing the sequences of all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the sequence of the claimed polynucleotide and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

C. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific, substantial, and credible" utilities. The Examiner is incorrect both as a matter of law and as a matter of fact.

1. The Precise Biological Role Or Function Of An Expressed Polynucleotide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise biological role or biological function of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological role or function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, Bedilion), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at

all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological role or function of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

2. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide in the family of expressed polypeptides, the Examiner refused to impute the utility of the members of the family of expressed polypeptides to PAWES-2.

In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did

not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses PAWES-2 as if the general class in which it is included is not the family of expressed polypeptides, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the family of expressed polypeptides do not. The family of expressed polypeptides is sufficiently specific to rule out any reasonable possibility that PAWES-2 would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the family of expressed polypeptides have any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the PAWES-2 encoded by the claimed polynucleotide is useful. It follows that the claimed polynucleotide also is useful.

3. Because the uses of the claimed polynucleotide in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. [Bedilion Declaration at ¶ 15.]

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include diagnostic assays (e.g., pages 38-41) and chromosomal mapping (e.g., pages 41-42).

4. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

While the Examiner has cited literature (Bowie et al., Burgess et al., and Lazar et al.) identifying some of the difficulties that may be involved in predicting protein function, none suggests that functional homology cannot be inferred by a reasonable probability in this case. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

Careful review of the Bowie et al. reference reveals that the teachings of Bowie et al. are directed primarily toward studying the effects of site-directed substitution of amino acid residues in certain proteins in order to determine the relative importance of these residues to protein structure and function. As discussed below in further detail, such experiments are not relevant to Applicants' use of amino acid sequence homology to reasonably predict protein function.

In support of Applicants' use of amino acid sequence homology reasonably to predict the utility of the claimed polypeptide, Bowie et al. teach that evaluating sets of related sequences, which are members of the same gene family, is an accepted method of identifying functionally important residues that have been conserved over the course of evolution (Bowie et al., page 1306, 1st column, last paragraph, and 2d column, 2nd full paragraph; page 1308, 1st column, last paragraph; page 1310, 1st column, last paragraph). It is known in the art that natural selection acts to conserve protein function. As taught by Bowie et al., proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits these substitutions to occur. Conversely, mutations that reduce or abolish protein function are eliminated by natural selection.

The Examiner further cited Lazar et al. and Burgess et al. as demonstrating "[t]he sensitivity of proteins to alterations of even a single amino acid in a sequence." (Office Action, page 7.) However, these references are not relevant to the case at hand. Lazar et al. describe the mutagenesis of two amino acid residues that are highly conserved among EGFs and TGFs. Similarly, Burgess et al. describe mutagenesis of HBGF-1 at an amino acid residue known to be important for ligand binding. In both of these cases, particular amino acid residues with known importance to protein function were

specifically targeted for site-directed mutagenesis. These mutations were "artificially" created in the laboratory and, therefore, are **not** analogous to molecular evolution, which is profoundly influenced by natural selection. For example, the deactivating mutations as described by Lazar et al. and Burgess et al. would almost certainly not be tolerated in nature. Furthermore, it is clear that over the course of evolution, amino acid residues that are critical for protein function are **conserved**. Therefore, the teachings of Lazar et al. and Burgess et al. are not relevant to the case at hand.

One could then argue that partial loss-of-function mutations do occur in nature, for example, the mutation in hemoglobin that causes sickle cell anemia. However, this example is the **rare** exception in evolution, **not the rule**. Persistence of such a mutation in a population would **not** be expected by one of ordinary skill in the art. Persistence occurs only because of the fluke of heterozygous advantage. Therefore, the Examiner's assertion that one of skill in the art would routinely expect to find single amino acid substitutions that drastically affect the function of the individual members of a conserved protein family is entirely unsubstantiated. Furthermore, in those rare cases where a partial loss-of-function mutation is persistent, the fact remains that the mutant polypeptide **still retains the utility of the non-mutant polypeptide**. The utility of the mutant polypeptide is the same as that of the non-mutant polypeptide, even though the results achieved are not equivalent. **Some** utility, not **perfect** utility, is all that is statutorily required for patentable utility.

The Examiner alleged that "it is well known in the art that even a single amino acid change will change the structure and the function of a protein." (Office Action, page 7.) However, in a recent Federal Circuit decision (Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corporation and Schering Corporation; CAFC 02-1026, -1027, February 21, 2003), the Court stated that "the uncontroversial fact that even a single nucleotide or amino acid substitution may drastically alter the function of a gene or protein is not evidence of anything at all. The mere possibility that a single mutation could affect biological function cannot as a matter of law preclude an assertion of equivalence."

The literature cited by the Examiner is not inconsistent with the Applicants' proof of homology by a reasonable probability. It may show that Applicants cannot prove function by homology with **certainty**, but Applicants need not meet such a rigorous standard of proof. Under the applicable law,

once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not made such a showing and, as such, the Examiner's rejection should be withdrawn.

5. Irrelevance of disease association to utility in toxicology testing

The Examiner argues on pages 5 and 8 of the Office Action that the specification does not disclose whether the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide, is associated with any disease. This is irrelevant. Applicants need not demonstrate whether the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide is associated with any disease, only whether the claimed polynucleotide is useful. The claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide is useful whether or not the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide is associated with any disease.

The claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide can be used for toxicology testing in drug discovery without any knowledge of disease association of the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide. Monitoring the expression of the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polynucleotide or polypeptide, regardless of the disease association of the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide. The claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide is useful for measuring the toxicity of drug candidates specifically targeted to **other** polynucleotides or polypeptides regardless of any possible utility for measuring the properties of the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide.

D. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to withdraw the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.C.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. *See supra* § III.C.2. Thus the Training Materials cannot be applied consistently with the law.

IV. Rejection of Claims 3-7, 9-10, 12-13, and 49 Under 35 U.S.C. § 112, first paragraph, enablement

A. Rejection of Claims 3-7, 9-10, 12-13, and 49 Because of Alleged Lack of Utility

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

B. Additional Rejection of Claims 3-7 and 9-10

Claims 3-7 and 9-10 were rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification "while being enabling for a polynucleotide comprising SEQ ID NO:4, does not reasonably provide enablement for a polynucleotide encoding SEQ ID NO:3 or a method of making SEQ ID NO:3." (Office Action, page 9).

The Office Action asserts that "[b]ecause SEQ ID NO:4 is simply a polynucleotide fragment, it is not possible to determining [*sic*] what the ATG start site of any protein might be and it cannot be determined if the sequence would be in-frame to encode any protein" (Office Action, page 10). These assertions ignore the disclosure of the specification. For example, the exact amino acid sequence of the polypeptide encoded by the SEQ ID NO:4 polynucleotide is explicitly set out as SEQ ID NO:3 in the Sequence Listing, and is also disclosed in Figures 2A, 2B, 2C, 2D, and 2E. In addition, Figures 2A, 2B, 2C, 2D, 2D, and 2E delineate the precise ATG start site and translation frame for the translation of the SEQ ID NO:3 polypeptide encoded by the SEQ ID NO:4 polynucleotide. Based on the disclosure in the specification, there is no need for one of skill in the art to "determine what the ATG start site" might be, or "if the sequence would be in-frame to encode any protein," because such determinations have already been provided by the patent application.

Furthermore, the Office Action asserts that "[o]ne cannot extrapolate the teaching of the specification to the scope of the claims because there is no teaching of whether any protein product is actually produced **in vivo**" (Office Action, page 10, emphasis in original). The Office Action then sets forth the novel theory that the central dogma of molecular biology (i.e., DNA directs transcription of

messenger RNA which in turn directs translation of protein) somehow does not apply to the discoveries of the present application. That is, the nucleotide sequence of SEQ ID NO:4 (which encodes the polypeptide of SEQ ID NO:3) was determined from sequences from human cDNA libraries. Those cDNA libraries in turn were made from messenger RNA isolated from human tissue. See the Specification, for example, at page 17, lines 10-15 and page 44, lines 1-2. Thus, the polynucleotide sequence of SEQ ID NO:4 is an **expressed** sequence. The Office Action purports that the existence of an expressed mRNA does not insure that the protein encoded by the mRNA will be translated and, hence, the claimed subject matter is not enabled by the specification.

Regulation of gene expression occurs at many levels, including transcription, splicing, polyadenylation, mRNA stability, mRNA transport and compartmentalization, translation efficiency, protein modification, and protein turnover. While steady state mRNA levels are not always directly proportional to the amount of protein in a cell, mRNA levels are **routinely** used as an indicator of protein expression. Countless scientific publications have been based on data relating to mRNA levels when the polypeptide encoded by the mRNA was unknown or difficult to detect. Moreover, mRNA levels are **usually** a good indicator of protein levels in a cell. The Office Action cites Alberts et al. (Molecular Biology of the Cell, 3rd edition (1994) page 465), Shantz et al. (Int. J. Biochem. Cell Biol.,1999, 31:107-122), McClean et al. (Eur. J. Cancer, 1993, 29A:2243-2248), and Fu et al. (EMBO J., 1996, 15:4392-4401) as examples of protein regulation downstream of transcription; however, these examples represent comparatively unusual mechanisms of gene regulation. According to B. Lewin [Genes VI (1997) Oxford University Press, Inc., New York, NY; Reference No. 7] (pages enclosed):

> Transcription of a gene in the active state is controlled at the stage of initiation, that is, by the interaction of RNA polymerase with its promoter. This is now becoming susceptible to analysis in the *in vitro* systems... ***For most genes, this is a major control point; probably it is the most common level of regulation***. [page 847, emphasis added].

> But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that ***the overwhelming majority of regulatory events occur at the***

initiation of transcription. Regulation of tissue-specific gene transcription lies at the heart of eukaryotic differentiation [pages 847-848, emphasis added].

Thus, the question is not whether there is the potential for post-transcriptional regulation of SEQ ID NO:3 expression, but rather, whether one skilled in the art would have a reasonable expectation that SEQ ID NO:3 expression correlates with the levels of SEQ ID NO:4 mRNA. In the case of the instant invention, one skilled in the art would be imprudent in assuming, *a priori*, that protein levels did not correspond to mRNA levels and that levels of SEQ ID NO:3 were controlled predominantly in a post-transcriptional manner, thereby dismissing the significance of mRNA levels.

The Office Action further cites Jansen et al. (Pediatric Res., 1995, 37:681-686) as evidence that "the regulation of mRNA translation is one of the major regulatory steps in the control of gene expression" (Office Action, page 10). However, the Jansen reference does not provide convincing evidence to contradict that, for most genes, initiation of transcription is the "major control point: probably it is the most common level of regulation" (Lewin, page 847). The Lewin reference would lead one of skill in the art to conclude that mRNA levels can **routinely** be used as an indicator of protein expression, and that mRNA levels are **usually** a good indicator of protein levels in a cell. Inasmuch as the predictive value of mRNA levels applies to the enablement of Applicants' invention, Applicants request withdrawal of the rejection.

In any case, it is academic whether Applicants have shown that the SEQ ID NO:3 polypeptide is actually expressed in any specific human tissue because there is no statutory requirement that an invention actually be reduced to practice to be patentable. The amino acid sequence of the polypeptide of SEQ ID NO:3 has been explicitly disclosed in the specification, thus satisfying the statutory requirements by a constructive reduction to practice. In conjunction with the disclosure in the specification and the knowledge in the art at the time the application was filed, the constructive reduction to practice of the polypeptide encoded by the claimed polynucleotides more than adequately provides enablement for the claimed invention.

C. Additional Rejection of Claims 3-4, 6-7, 9-10, and 12-13

The Examiner further contended that "the specification, while being enabling for a polynucleotide comprising SEQ ID NO:4 and the complete complement thereof does not reasonably provide enablement for polynucleotides encoding naturally occurring amino acid sequences at least 90% identical to the amino acid sequence of SEQ ID NO: 3, encoding polypeptides having the amino acid sequence of SEQ ID NO:3, encoding a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:3 having biological or immunogenic activity, naturally occurring polynucleotides having at least 90% identity to SEQ ID NO:4, polynucleotides complementary to SEQ ID NO:4 or said naturally occurring polynucleotide with at least 90% identity to SEQ ID NO:4 or fragments of SEQ ID NO:4." (Office Action, page 11.) The Examiner states that "[t]he specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with these claims." (Office Action, pages 11-12.)

The claimed polynucleotides are enabled, i.e., they are supported by the Specification and what is well known in the art.

1. How to make

SEQ ID NO:3 and SEQ ID NO:4 are specifically disclosed in the application (see, for example, pages 60-61 of the Sequence Listing). Variants of SEQ ID NO:3 and SEQ ID NO:4 are described, for example, on page 3, lines 9-11, page 3, line 29 through page 4, line 6, page 15, line 27 through page 16, line 5, page 18, lines 1-4 and 11-21. Incyte clones in which the nucleic acids encoding the human PAWES-2 were first identified and libraries from which those clones were isolated are disclosed, for example, on page 17, lines 10-15 and page 44, lines 1-2. Chemical and structural features of PAWES-2 are disclosed, for example, on page 17, lines 16-24. Examples of SEQ ID NO:3 and SEQ ID NO:4 fragments are given on page 17, lines 24-26.

The Examiner alleged that "even a single amino acid substitution or what appears to be an inconsequential modification will often dramatically affect the biological activity and characteristic of a protein," and "the specification has not shown that variant polynucleotides or polynucleotides encoding polypeptides produced by variants of polynucleotides encoding SEQ ID NO:3 or polynucleotides

comprising fragments of SEQ ID NO:4 are capable of functioning as that which is suggested." (Office Action, pages 12-13.) However, Applicants submit that the polypeptide variant sequences and polynucleotide variant sequences are described by their being "naturally occurring" and by their percentage sequence identity with SEQ ID NO:3 and SEQ ID NO:4 and not by biological activity or biological "function." The choice of amino acids or nucleotides to alter is made by nature. "Naturally occurring" polypeptide variant sequences and polynucleotide variant sequences occur in nature; they are not created exclusively in a laboratory. The Specification teaches how to find polynucleotide variants (e.g., page 38, line 27 through page 39, line 1) which can then be expressed to make polypeptide variants and how to determine whether a given naturally occurring polynucleotide sequence falls within the "at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4" scope and whether a given naturally occurring amino acid sequence falls within the "at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3" scope (e.g., page 11, lines 5-21 and page 45, lines 2-19). In addition, determination of percent identity is well known in the art.

For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the specification of the instant application. See, e.g., page 19, lines 17-21; page 20, lines 1-28; page 38, line 12 to page 39, line 9; and Example VI at pages 50, line 23 through page 51, line 8. Thus, one skilled in the art need not make and test vast numbers of polynucleotides that encode polypeptides based on the amino acid sequence of SEQ ID NO:3, or vast numbers of polynucleotides based on the polynucleotide sequence of SEQ ID NO:4. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides, and their encoded polypeptides, that already exist in nature. By adjusting the nature of the probes or nucleic acids (i.e., non-conserved, conserved, or highly conserved) and the conditions of hybridization (maximum, high, intermediate, or low stringency), one can obtain variant polynucleotides of SEQ ID NO:4 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:3 recited by the present claims using conventional techniques of recombinant protein production. By extension, one of skill in art could make fragments of naturally

occurring polynucleotides at least 90% identical to SEQ ID NO:4, and could use such fragments, for example, as hybridization probes to detect full-length naturally occurring polynucleotides at least 90% identical to SEQ ID NO:4.

The making of the claimed polynucleotide by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 19, lines 11-16, page 21, lines 9-14, and page 21, lines 23-26. The making of the claimed polynucleotide comprising a complementary sequence is disclosed in the Specification at, e.g., page 31, lines 24-29, page 32, lines 13-24, page 33, lines 9-17, and page 52, lines 1-10.

Furthermore, in order to expedite prosecution, Claim 12 has been amended to recite:

> An isolated polynucleotide selected from the group consisting of. . . :
> c) a polynucleotide having a sequence completely complementary to a polynucleotide of a) over the entire length of the polynucleotide of a), and
> d) a polynucleotide having a sequence completely complementary to a polynucleotide of b) over the entire length of the polynucleotide of b).

In order to expedite prosecution, Claim 3 has been amended so that polynucleotides encoding a "biologically active fragment" are no longer recited. Therefore the rejection on the basis of polynucleotides encoding biologically active fragments of SEQ ID NO:3 is moot.

Applicants submit that the specification fully enables the making of the claimed polynucleotide encoding an immunogenic fragment of SEQ ID NO:3. The polypeptide sequence of SEQ ID NO:3 is provided in the Sequence Listing. Preparation of immunogenic fragments is described in the Specification, e.g., at page 30, lines 8-14 and page 55, lines 8-17.

The ability of a given fragment to induce a specific immune response in animals or cells, or to bind with specific antibodies (See Specification at, e.g., page 9, lines 3-6, and page 55, lines 5-21) are tests for whether the fragment is "immunogenic." The tests of fragments by these methods do not require undue experimentation; the specification provides a test for antibody binding e.g., at page 43, lines 13-16.

This satisfies the "how to make" requirement of 35 U.S.C. § 112, first paragraph.

2. How to Use

The claimed polynucleotide variants, fragments, and complementary sequences are products of expressed genes. Therefore, these polynucleotides are useful for the same purposes as the polynucleotides comprising the polynucleotide sequence of SEQ ID NO:4 and the polynucleotide encoding the polypeptide sequence of SEQ ID NO: 3. These utilities are described fully under the rejection under §101 (*supra*) of this Response and in the Bedilion Declaration. In addition, the Specification discloses the use of complementary polynucleotides in antisense technology e.g., on page 8, line 25 through page 9, line 1, page 31, lines 22-29, page 32, lines 14-24, and page 52, lines 1-10. This satisfies the "how to use" requirement of 35 U.S.C. § 112, first paragraph.

The Examiner further cited Bowie et al., Burgess et al., and Lazar et al. in support of the argument that the claimed variant polynucleotides and recited variant polypeptides may have different biological functions than SEQ ID NO:4 and SEQ ID NO:3.

However, these documents do not support the enablement rejection as the Specification, along with what is well known to one of skill in the art, enable the use of the claimed polynucleotide in toxicology testing by virtue of their being expressed polynucleotides, regardless of their biological function. The Examiner has confused use with biological function.

The Office Action asserts that "the specification has not shown that [the claimed polynucleotides] are capable of functioning as that which is suggested" because "even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein" (Office Action, page 13). This is incorrect. One of skill in the art would reasonably conclude that the claimed polynucleotides encode polypeptide variants having the functions of the polypeptide of SEQ ID NO:3. However, in a recent Federal Circuit decision (Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corporation and Schering Corporation; CAFC 02-1026, -1027, February 21, 2003), the Court stated that "the uncontroversial fact that even a single nucleotide or amino acid substitution may drastically alter the function of a gene or protein is not evidence of anything at all. The mere possibility that a single mutation could affect biological function cannot as a matter of law preclude an assertion of equivalence."

While it may be true that some amino acid substitutions can dramatically affect biological activity of a protein, the recited polypeptide variants encoded by the **claimed** polynucleotides have naturally occurring amino acid sequences, and natural selection acts to conserve protein function. For example, as taught by Bowie et al. (Science, 1990, 247:1306-1310; cited by the Office Action), proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits these substitutions to occur. Conversely, mutations that reduce or abolish protein function are eliminated by natural selection. Based on these central tenets of molecular evolution, Applicants submit that the amino acid differences between the SEQ ID NO:3 polypeptide and the recited polypeptide variants comprising naturally occurring amino acid sequences at least 90% identical to SEQ ID NO:3 are likely to occur at positions of minimal functional importance, while residues conserved are likely those that are important for protein function.

The Office Action cites Bowie et al. (*supra*), Burgess et al. (J. Cell Biol., 1990, 111:2129-2138), and Lazar et al. (Mol. Cell Biol., 1998, 8:1247-1252) in support of the Patent Office's assertions. The Office Action has applied a limited subset of the results taught by these references, and has refused to consider the teachings of these references as a whole. Based on this limited analysis, the Office Action has concluded that "the specification has not shown that [the claimed polynucleotides] are capable of functioning as that which is suggested" (Office Action, page 13).

Burgess et al. describe mutagenesis of HBGF-1 at an amino acid residue known to be important for ligand binding, and show that this mutation is unable to completely eliminate the biological activity of the wild-type HBGF-1 protein (see, e.g., Burgess et al., abstract). Therefore, one of skill in the art would still be able to use these altered polypeptides **in the exact same manner as one would use the nonaltered polypeptides**, even though the results would not be exactly the same as if the nonaltered polypeptides were used.

Similarly, Lazar et al. discloses the results of making seven different mutations in TGF-alpha at either residue 47 or 48 (e.g., at Table 1 on page 1250). Only one of these mutations, the mutation of leucine 48 to alanine, results in a complete loss of function. The other six mutations result in polypeptide variants that can be used in exactly the same way as the wild-type polypeptide can be used, albeit the results of such use would not be identical. Residue 48 is one of 11 amino acids (from a

total of 50) which are conserved among members of the EGF-like growth factors (Figure 1 of Lazar et al., page 1248). Thus, it is significant that only one out of the three mutations made at this conserved amino acid residue results in complete loss of TGF-alpha activity (Table 1 of Lazar et al., page 1250). Considering the teachings of Lazar et al. as a whole, one of skill in the art would recognize that polypeptide variants would more likely than not retain the function of the wild-type polypeptide.

One of skill in the art, considering the references cited by the Office Action as a whole, would understand how to use the recited variants of SEQ ID NO:3; even if the results achieved from using the recited variants were not equivalent to the results achieved from using the SEQ ID NO:3 polypeptide, one of skill in the art would still be able to achieve **some** level of results by using the recited variants in the same manner as the SEQ ID NO:3 polypeptide. This is all that is required to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

With respect to the claimed fragments, one of skill in the art could make and use the claimed polynucleotide fragments, and the claimed polynucleotides encoding the recited polypeptide fragments, without undue experimentation, based on the specification and the state of the art at the time the application was filed. For example, one of skill in the art would know how to use the claimed polynucleotide fragments, and polynucleotides encoding the recited polypeptide fragments, as hybridization probes or PCR probes to detect the presence of a polynucleotide comprising SEQ ID NO:4 (Specification, e.g., page 19, lines 17-21; page 20, lines 6-28, page 38, line 12 to page 39, line 9; and Example VI at pages 50-51). As discussed above, it is not necessary for a polynucleotide fragment to encode a functional polypeptide for one of skill in the art to be able to use that polynucleotide fragment without undue experimentation.

The Office Action further asserts that "the claims as written are drawn to encoded fragments with no identity to SEQ ID NO:3 because they are drawn to fragments of a polypeptide which comprises SEQ ID NO:1 [*sic*: SEQ ID NO:3]" (Office Action, page 14). Applicants respectfully disagree. Nevertheless, to expedite prosecution, claim 3 has been amended to clarify the subject matter of the invention. For example, claim 3 now recites "c) an immunogenic fragment of a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, wherein said fragment is at least five amino acid residues in length." Support for

this amendment can be found in the specification at, for example, page 7, lines 23-26 and page 30, lines 8-14. For example, the specification explicitly describes a polypeptide comprising an immunogenic fragment of SEQ ID NO:3 by stating that "[s]hort stretches of PAWES amino acids may be fused with those of another protein, such as KLH" (page 30, lines 13-14).

Furthermore, the Office Action states that "it would not be possible to determine with any predictability whether, for example, the antibodies produced from the claimed immunogenic fragment that could be derived from SEQ ID NO:3 will actually bind to SEQ ID NO:3" (Office Action, page 13). The specification defines immunologically active (a synonym for immunogenic) as "the capability of the natural, recombinant, or synthetic PAWES, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies." (e.g., at page 9, lines 4-6). Therefore, the recited immunogenic fragments, encoded by the claimed polynucleotides, are those fragments which can induce a specific immune response and bind with specific antibodies. One of skill in the art would know how to make polynucleotides encoding immunogenic fragments, and could use the claimed polynucleotides, for example, as hybridization and/or PCR probes to detect polynucleotides encoding the SEQ ID NO:3 polypeptide. One of skill in the art would also know how to use such polynucleotides, for example, in toxicology testing for drug discovery.

The disclosure in the specification regarding the production of antibodies is broad. For example, the specification at page 29, lines 23-25 discloses that "purified PAWES may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind PAWES. Antibodies to PAWES may also be generated using methods that are well known in the art." As the Examiner recognizes, it is well known in the art that "it is possible to produce antibodies to almost any part of an antigen" (Office Action, page 13). Thus, there is no doubt that it would be routine for one of skill in the art to produce antibodies using fragments of PAWES-2 (SEQ ID NO:3).

The specification also discloses methods of screening antibodies for specific immunogenic properties, for example, at page 31, lines 13-20:

> Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between PAWES and its specific antibody. A

> two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering PAWES epitopes is preferred, but a competitive binding assay may also be employed. (Maddox, supra.)

Therefore, based on the disclosure in the specification and the state of the art at the time the application was filed, it would have been routine for one of skill in the art to make antibodies using fragments of SEQ ID NO:3 and to determine which of the resulting antibodies could bind to PAWES-2, without undue experimentation.

The Office Action cites references that demonstrate that it may be difficult to predict which portions of intact proteins constitute epitopic regions which could provoke an immune response. (Holmes, Exp. Opin. Invest. Drugs, 2001, 10(3):511-519; Roitt et al., Immunology, 4th ed., Mosby, London (1998). However, it is not necessary to accurately predict epitopes in order to make and/or use the recited immunogenic fragments of SEQ ID NO:3. The cited references have no bearing on the ability of a skilled artisan to make antibodies to PAWES-2 fragments, and screen these antibodies for their ability to bind PAWES-2, without undue experimentation.

For at least the above reasons, the specification enables one of skill in the art to make and use the recited immunogenic fragments of SEQ ID NO:3.

With respect to the claimed complements, the Office Action asserts that the claimed polynucleotides include not only "completely" complementary polynucleotides, "but also, because the term 'partial' is unlimited and undefined, includes a substantial number of species which lack significant complementarity to the claimed polynucleotides" (Office Action, pages 14-15). Applicants respectfully point out that the term "partial" is not recited in the claims. Nevertheless, to expedite prosecution, Claim 12 has been amended such that the recited polynucleotide complements are "completely complementary" to the recited polynucleotides "over the entire length" of the polynucleotides.

Furthermore, the Office Action asserts that "it would be expected that a substantial number of the complementary polynucleotides encompassed by the claims **would not** share either structural or functional properties with polynucleotides that encode SEQ ID NO:3 or encode proteins that share either structural or functional properties with SEQ ID NO:3." (Office Action, page 15; emphasis in original). Applicants respectfully submit that all of the claimed complementary polynucleotides would

share **structural** properties with polynucleotides of SEQ ID NO:4. Thus, one of skill in the art could make and use the claimed complementary polynucleotides, without undue experimentation, based on the specification and the state of the art at the time the application was filed. For example, one of skill in the art would know how to use the claimed complementary polynucleotides as hybridization probes or PCR probes to detect the presence of a polynucleotide comprising SEQ ID NO:4 (Specification, e.g., page 19, lines 17-21, page 20, lines 6-28, page 38, line 12 to page 39, line 9, and Example VI at pages 50-51). As discussed above, it is not necessary for a complementary polynucleotide to share "functional properties with polynucleotides that encode SEQ ID NO:3" for one of skill in the art to be able to use that complementary polynucleotide without undue experimentation. One of skill in the art would also know how to use such polynucleotides, for example, in toxicology testing for drug discovery.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Office Action has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited polynucleotides. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited polynucleotides.

For at least the above reasons, Applicants respectfully request that the enablement rejections be withdrawn.

V. Rejection of Claims 3-4, 6-7, , 9-10, and 12-13 Under 35 U.S.C. § 112, first paragraph, written description

Claims 3-4, 6-7, , 9-10, and 12-13 have been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. The Examiner alleged that "[t]he written description in this case only sets forth SEQ ID NO:4 and the complete complement thereof and therefore the written description is not commensurate in scope with the claims drawn to polynucleotides encoding naturally occurring amino acid sequences at least 90% identical to the amino acid sequence of SEQ ID NO:3, encoding polypeptides having the amino acid sequence of SEQ ID NO:3, encoding a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:3, wherein the fragment has biological activity, encoding immunogenic fragments of SEQ ID NO:3, naturally occurring polynucleotides having at least 90% identity to SEQ ID NO:4, polynucleotides complementary to SEQ ID NO:4 or said naturally occurring polynucleotide with at least 90% identity to SEQ ID NO:4." (Office Action, pages 15-16.)

In order to expedite prosecution, Claim 3 has been amended so that polynucleotides encoding a "biologically active fragment" are no longer recited. Therefore the rejection on the basis of polynucleotides encoding biologically active fragments of SEQ ID NO:3 is moot.

The Office Action states that "[a]bsent evidence to the contrary, the sequence elected for examination is deemed to be an incomplete cDNA. Because the cDNA that corresponds to the SEQ ID NO mentioned in the claim is not full-length, a sequence prepared from undefined parts of a cDNA clone will not comprise the entire coding region of any particular gene, nor is it clear the partial sequence is even in frame to encode a polypeptide" (Office Action, page 16).

SEQ ID NO:4, however, encompasses a complete coding region of a gene, and this coding region encodes a polypeptide of SEQ ID NO:3. It is axiomatic that a polynucleotide of SEQ ID NO:4 encodes a polypeptide of SEQ ID NO:3. One of ordinary skill in the art would be able to routinely determine the extent of the coding region of SEQ ID NO:4 by looking for start codons and stop codons sharing the same reading frame in the polynucleotide. Translation of the limited number of possible coding regions of SEQ ID NO:4 would reveal which one corresponds to the polypeptide sequence disclosed in SEQ ID NO:3. All of these determinations are routine in the art, and do not

require undue experimentation. Thus, Applicants had full possession of not only SEQ ID NO:4 and SEQ ID NO:3 at the time of filing, but also the coding region of SEQ ID NO:4 which encodes SEQ ID NO:3. It is well known to one of ordinary skill in the art that the coding region of a gene can be used to produce the encoded polypeptide, whether or not the 5' and 3' regulatory regions and untranslated regions are present. For example, the coding sequence of SEQ ID NO:4 could be cloned into an expression vector and the coding sequence expressed in an appropriate host organism. For example, the specification discloses that "[f]or expression of PAWES in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element." (e.g., at page 52, lines 14-18).

The Office Action also alleges that Applicants did not possess the claimed invention because polynucleotides comprising SEQ ID NO:4 include "full length" genes which are not adequately disclosed in the specification. That is, the Office Action asserts that the 5' and 3' regulatory regions and untranslated regions of the gene must be described to fulfill the written description requirements. Such a position is improper.

Applicants respectfully point out that these "full length" genes are not explicitly recited in the claims. Only the specific polynucleotides recited in the claims are at issue, and these polynucleotides are adequately described in the specification. Although the phrase "comprising" "does not exclude additional, unrecited elements or method steps" (M.P.E.P. § 2111.03), the use of this phrase does not result in the inclusion of any arbitrary element in the scope of the claim if such elements are not specifically recited. In this case, the claimed polynucleotides **do not** explicitly include the 5' and 3' regulatory regions and untranslated regions of the gene, and Applicants **are not** explicitly claiming the "full length" gene (although Applicants are hereby **not** expressly disclaiming the "full length" gene, or any polynucleotide including the 5' or 3' regulatory regions or untranslated regions of the gene). There is simply no requirement for the specification to include a detailed description of elements which are not explicitly recited by the claims.

The Office Action states that "for examination purposes, the 'naturally occurring' sequences are understood to be drawn to allelic variants of the claimed sequence" (Office Action, page 16). The Patent Office has improperly attempted to impose its own view of what the invention is, without regard to Applicants' disclosure in the specification. As stated in the M.P.E.P., "claims must be 'given the broadest reasonable interpretation consistent with the specification.' " (M.P.E.P. § 2111). In this case, naturally occurring sequences are not limited only to those sequences which are allelic variants of SEQ ID NO:4. Based on the principle that "the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification" (M.P.E.P. § 2111.01), the phrase "naturally occurring sequence" should be understood to include any sequence that **occurs in nature**. Support for this meaning can be found in the specification, which states that PAWES-2 can be "obtained from **any species**, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and preferably the human species, from any source, whether **natural**, synthetic, semi-synthetic, or recombinant." (e.g., at page 6, lines 20-22; emphasis added). It is improper for the Patent Office to impose its own narrow definition of what the invention is, and then conduct the examination based on this incorrect definition.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of

> such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:3 and SEQ ID NO:4 are specifically disclosed in the application (see, for example, pages 60-61 of the Sequence Listing). Variants of SEQ ID NO:3 are described, for example, at page 15, line 27 through page 16, line 5. In particular, the preferred, more preferred, and most preferred SEQ ID NO:3 variants (80%, 90%, and 95% amino acid sequence identity to SEQ ID NO:3) are described, for example, at page 18, lines 1-4. In particular, the preferred, more preferred, and most preferred SEQ ID NO:4 variants (80%, 90%, and 95% polynucleotide sequence identity to SEQ ID NO:4) are described, for example, at page 18, lines 11-21. Incyte clones in which the nucleic acids encoding the human PAWES-2 were first identified and libraries from which those clones were isolated are described, for example, at page 17, lines 10-15 of the Specification. Chemical and structural features of PAWES-2 are described, for example, on page 17, lines 16-24. Given SEQ ID NO:3, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:3 having at least 90% sequence identity to SEQ ID NO:3. Given SEQ ID NO:4, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:4 having at least 90% sequence identity to SEQ ID NO:4. The Specification describes (e.g., page 11, lines 5-21 and page 45, lines 2-19) how to use BLAST and other methods to determine whether a given sequence falls within the "at least 90% identical" scope. Immunogenic fragments are described in the Specification, e.g, at page 9, lines 2-6.

There simply is no requirement that the claims recite particular variant and fragment polypeptide or polynucleotide sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polypeptide variants and fragments are defined in terms of SEQ ID NO:3 ("An isolated polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of. . . b) a naturally occurring polypeptide comprising an amino acid

sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, and c) an immunogenic fragment of a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, wherein said fragment is at least five amino acid residues in length." The polynucleotide variants and fragments are defined in terms of SEQ ID NO:4 ("An isolated polynucleotide selected from the group consisting of . . . b) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4;" "An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 12.")

Because the recited polypeptide variants and fragments are defined in terms of SEQ ID NO:3, and the recited polynucleotide variants and fragments are defined in terms of SEQ ID NO:3 and SEQ ID NO:4, the precise chemical structure of every polypeptide variant and fragment and every polynucleotide variant and fragment within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Applicants to unduly limit the scope of their claimed invention. Applicants further submit that given the polypeptide sequence of SEQ ID NO:3 and the polynucleotide sequence of SEQ ID NO:4, it would be redundant to list specific fragments. The structures of SEQ ID NO:3 and SEQ ID NO:4 provide the blueprint for all fragments thereof. Listing all possible fragments of SEQ ID NO:3 and SEQ ID NO:4 is, thus, a superfluous exercise which would needlessly clutter the Specification. Examples of SEQ ID NO:3 and SEQ ID NO:4 fragments are given on page 17, lines 24-26. Accordingly, the Specification provides an adequate written description of the recited polypeptide and polynucleotide sequences.

A. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human

fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent Claims 3 and 12 recites chemical structure to define the claimed genus:

> 3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:
>
> a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3,
>
> b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, and
>
> c) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, wherein said fragment is at least five amino acid residues in length.
>
> 12. An isolated polynucleotide selected from the group consisting of:
>
> a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4,
>
> b) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4,
>
> c) a polynucleotide having a sequence completely complementary to a polynucleotide of a) over the entire length of the polynucleotide of a), and
>
> d) a polynucleotide having a sequence completely complementary to a polynucleotide of b) over the entire length of the polynucleotide of b).

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:3 and SEQ ID NO:4. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides or polypeptides recited by the claims. Moreover, such functional recitations as are included add to the structural characterization of the recited polynucleotides and polypeptides. The polynucleotides and polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever

is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

B. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." (Office Action, page 18.) Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078; Reference No. 8). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to PAWES-2 proteins related to the amino acid sequence of SEQ ID NO:3. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as PAWES-2 proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:3. The "variant language" of the present claims recites, for example, polypeptides encoding "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:3" (note that SEQ ID NO:3 has 332 amino acid residues). This variation is far less than that of all potential PAWES-2 proteins related to SEQ ID NO:3, i.e., those PAWES-2 proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:3.

C. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of April 29, 1998. Much has happened in the development of recombinant DNA technology in the 18 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:3 and SEQ ID NO:4, and the additional extensive detail provided by the subject application, the present inventors were in possession of the recited polynucleotides and polypeptides at the time of filing of this application.

D. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:3 or SEQ ID NO:4. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides and polypeptides defined by the present claims is adequately

described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the written description rejection.

VI. Rejection of Claims 12-13 Under 35 U.S.C. § 112, second paragraph

The Examiner rejected Claims 12-13, alleging that "Claim 12 and dependent claims [*sic*] 13 are indefinite because claim 12 recites the phrase 'equivalent of.' The phrase is confusing because it is not clear what is meant by an 'equivalent.'" (Office Action, page 19.)

Applicants have amended Claim 12 to delete the phrase "an RNA equivalent of a)-d)." The word "polynucleotide" covers both DNA and RNA (See e.g., Specification, page 12, lines 25-29) and therefore the claim as amended covers both DNA and RNA in any case.

VII. Rejection of Claims 3, 6, 7, and 9 Under 35 U.S.C. § 102(e) as Being Anticipated By U.S. Patent No. 5,683,898

The Examiner rejected Claims 3, 6, 7, and 9 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,683,898. In order to expedite prosecution, Claim 3 has been amended to recite:

> . . .
>
> c) an immunogenic fragment of a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, wherein said fragment is at least five amino acid residues in length.

Support for this amendment may be found in the specification at, e.g, page 7, lines 23-26 and page 30, lines 8-10. U.S. Patent No. 5,683,898 does not teach a polynucleotide encoding an immunogenic fragment of a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, wherein said fragment is at least five amino acid residues in length. Therefore, U.S. Patent No. 5,683,898 does not anticipate Claims 3, 6, 7, and 9,

and Applicants respectfully request that the Examiner withdraw the novelty rejection of Claims 3, 6, 7, and 9.

VIII. Rejection of Claim 12 Under 35 U.S.C. § 102(b) as Being Anticipated By the Boehringer Mannheim 1994 Catalog

The Examiner rejected Claim 12 under 35 U.S.C. §102(b) as being anticipated by the Boehringer Mannheim 1994 Catalog. In order to expedite prosecution, Claim 12 has been amended as follows:

> . . . c) a polynucleotide completely complementary to a polynucleotide of a) over the entire length of the polynucleotide of a),
> d) a polynucleotide completely complementary to a polynucleotide of b) over the entire length of the polynucleotide of b).

The Boehringer Mannheim 1994 Catalog does not teach a polynucleotide completely complementary to a polynucleotide of a) over the entire length of the polynucleotide of a) or a polynucleotide completely complementary to a polynucleotide of b) over the entire length of the polynucleotide of b). Therefore, the Boehringer Mannheim 1994 Catalog does not anticipate Claim 12, and Applicants respectfully request that the Examiner withdraw the novelty rejection of Claim 12.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections and rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent at (650) 845-4646.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: March 31, 2003

Susan K. Sather

Susan K. Sather
Reg. No. 44,316
Direct Dial Telephone: (650) 845-4646

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

Enclosures:

1. John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999)
2. Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, (August 1997) Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947

3. Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999)

4. Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000)

5. John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999)

6. Email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding

7. B. Lewin, Genes VI (1997) Oxford University Press, Inc., New York, NY; pages 847-848

8. Brenner et al. Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 3, 4, 5, 9, and 12 have been amended as follows:

3. (Once Amended) An isolated polynucleotide encoding a polypeptide [of claim 1] selected from the group consisting of:

a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3,

b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, and

c) an immunogenic fragment of a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, wherein said fragment is at least five amino acid residues in length.

4. (Once Amended) An isolated polynucleotide of claim 3 encoding a polypeptide [of claim 2] comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3.

5. (Once Amended) An isolated polynucleotide of claim 4, comprising a polynucleotide [having a] sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4.

9. (Once Amended) A method for producing a polypeptide [of claim 1], the method comprising:

a) culturing the cell of claim 7 [a cell] under conditions suitable for expression of the polypeptide, [wherein said cell is transformed with a recombinant polynucleotide, and said recombinant

polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1,] and

b) recovering the polypeptide so expressed.

12. (Once Amended) An isolated polynucleotide [comprising a sequence] selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4,

b) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4,

c) a polynucleotide having a sequence completely complementary to a polynucleotide of a) over the entire length of the polynucleotide of a), and

d) a polynucleotide having a sequence completely complementary to a polynucleotide of b) over the entire length of the polynucleotide of b) [and

e) an RNA equivalent of a)-d)].